Chapter 9
Autoimmune Liver Disease

A1. Organize and convene an international, interdisciplinary research workshop on development of animal models of autoimmune liver diseases. The NIH Workshop on Primary Sclerosing Cholangitis (PSC) in September 2005 included a comprehensive presentation on animal models in this disease. (30%)

A2. Develop multicenter networks of investigators to study natural history, pathogenesis, etiology, and therapy of autoimmune liver diseases. Discussion among investigators is ongoing about the organizational and operational structure of such multicenter networks. (0%)

A3. Define the roles of CD4+ and CD8+ T cells, other effector immunocytes, dendritic cells, and the innate immune system in liver injury in humans (and animal models) with autoimmune liver disease. This is being addressed currently in the context of NIH-supported research projects. Human studies would be facilitated by autoimmune liver disease networks. (0%)

B1. Demonstrate whether high-dose ursodiol therapy is effective in retarding the progression of PSC and identify risk factors for progression and for response to treatment. The NIH sponsors a multicenter controlled trial of high-dose ursodiol in PSC, which completed its enrollment in late 2005. A similar study in Europe has demonstrated the lack of effect of high-dose ursodiol on survival or outcome (Olson R. *Gastroenterology* 2005; 129:1464). (30%)

B2a. Develop sensitive and specific biomarkers for disease activity and stage in PBC and PSC. The NIH has encouraged research in this area through its initiative on "Development of Disease Biomarkers" (PA-05-098). (0%)

B2b. Develop diagnostic criteria and standard definitions for endpoints of therapy. Discussions on developing standardized terminology and diagnostic criteria for liver and biliary diseases were started at an NIH/AASLD workshop on "Nomenclature, Diagnostic, and Outcome Criteria in Liver and Biliary Diseases" in November 2005 and at the September 2005 NIH Workshop on PSC. (10%)

B3a. Identify genetic linkages in PBC and refine the HLA associations in autoimmune hepatitis and PSC. This goal would be facilitated by the establishment of autoimmune liver disease networks. The NIH encourages research to refine understanding of the association of HLA with autoimmune liver diseases through its initiative on "HLA Region Genetics in Immune-mediated Diseases" (RFA-AI-04-039). (0%)

B3b. Develop animal models for each of the autoimmune liver diseases. Promising models have been developed for PSC (Mdr2-/- mouse: Popov Y. *J Hepatol* 2005:43:1045) and autoimmune hepatitis (TGFβ1 knockout mouse: Lin JT. Lab Invest 2005;85:550). A recent NIH initiative on "Animal Models of NIDDK-relevant Diseases" (PA-05-049) specifically encourages research to develop animal models of autoimmune liver diseases. (20%)

C1. Develop alternatives to prednisone/azathioprine as maintenance therapy of autoimmune hepatitis and define markers for when and how therapy can be safely stopped. The NIH sponsors an initiative on "Innovative Grants in Immune Tolerance" (RFA-AI-05-023), which encourages research on alternative maintenance therapy for autoimmune hepatitis. (0%)

C2. Develop sensitive serum markers for early detection of cholangiocarcinoma in PSC. The NIH sponsors a multicenter controlled trial of high-dose ursodiol in PSC in which serum and tissue samples are collected and stored for potential investigation of markers for early detection of cholangiocarcinoma. Additionally, the NIH encourages research in this area through its initiative on "Development of Disease Biomarkers" (PA-05-098). (0%)

C3. Identify modifiable environmental (with or without genetic) triggers for induction of autoimmune hepatitis (from human studies or murine models). In an NIH-funded multicenter study, risk factors for PBC were sought among a large collection of patients and controls; evidence for infectious and toxic exposures as triggers for PBC were found (Gershwin ME. *Hepatology* 2005; 42:1194). The NIH sponsors an initiative on "Innovative Grants in Immune Tolerance" (RFA-AI-05-023), which encourages research on triggers of autoimmune disease. (10%)

Figure 11. Estimated Progress on Autoimmune Liver Disease Research Goals, 2005 (Year 1)